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EXAMINER	
VOGEL, NANCY S	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/681,381	**Applicant(s)** SCHEMBRI ET AL.	
	Examiner Nancy T. Vogel	**Art Unit** 1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.
4a) Of the above claim(s) *16,17 and 26-32* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-15 and 18-25* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☒ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☒ Certified copies of the priority documents have been received in Application No. 09/301,704.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/1/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-32 are pending in the case.

Receipt of the Information Disclosure statement on 3/1/04 is acknowledged.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 1/6/05 is acknowledged. The traversal is on the ground(s) that the search required for examination of all groups would not be unduly burdensome, and further, that two of the Groups are placed in the same class, and that classification in different class and subclass does not indicate that a different search is required. This is not found persuasive because the examination of claims drawn to recombinant cells comprising a multifunctional adhesin protein, a method of removing a metal from an environment, and an isolated fimbrial structure, clearly are not the same or coextensive, and would constitute a burden. Furthermore, applicant's arguments regarding the classification of claims, it is noted that the search for biotechnological subject matter is not confined to the patent literature, but rather includes scientific journals and publications. Therefore, the classification of claims does not in itself show whether restriction is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 16, 17, and 26-32 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 1/6/05.

Sequence compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because sequences are set forth in the drawings (Fig. 1) and specification (Table 2) that lack sequence identifiers. It is often convenient to identify sequences in figures by amending the Brief Description of the Drawings section (see MPEP 244.02). If the sequences are already present in the sequence listing, it would be remedial to amend the Brief Description of the Drawings to include the appropriate sequence identifiers. Applicants should review the application carefully for sequences which have do not have a sequence identifier, or whose sequence is not listed in the CRF or Sequence Listing. Applicants are required to comply with all of the requirements of 37 CFR 1.821 - 1.825. Any response to this office action that fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F. R. 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6, 8, 9, 12-15 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Pallesen et al. (Microbiol., 141: 2839-2848, 1995) (cited by applicants).

Pallesen et al. describes recombinant cells expressing on its surface a multifunctional adhesin protein (FimH adhesin), containing at least one first kind of binding domain is a naturally occurring binding domain that binds to an organic receptor, and at least one second kind of binding domain that is not naturally present in the adhesin , which is capable of binding to a compound to which the naturally occurring adhesin protein substantially does not bind. The reference discloses peptide insertion into the extracellular domain to create new binding domains "without affecting compatibility with the ...adhesive ability" (p. 2840, 2nd column, 2nd paragraph) as recited by claims 1-4 and 12-14. The reference discloses the non-naturally occurring binding region is that of preS2 sector of the hepatitis B surface antigen or the epitope from cholera toxin (p. 2840, 2nd column, 2nd paragraph). The cholera toxin subunit is disclosed as binding 50-64 amino acids in length as required by claim 8 (p. 2841, 1st column, 1st paragraph). Fig. 3 (p. 2842) discloses that at least one histidine residue is present in the peptide sequence preS2 of less that 100 amino acids (claims 8, 9). Fig. 1 (p.2840) discloses plasmids utilized with the corresponding heterologous inserts. The population of recombinant cells recited in claim 18 are inherent to the method of generating described by Pallesen et al. (p. 2840, methods).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4, 6-10, 12-15, and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pallesen et al. (Microbiol., 141: 2839-2848, 1995) as applied to claims 1-4, 6, 8, 9, 12-15 and 18 above, in view of Sousa et al. (Nature Biotechnol., 14: 1017-1020, 1996).

Pallesen et al. is cited for the reasons set forth above.

Pallesen et al. does not teach a recombinant cell expressing on its surface a multifunctional adhesin protein containing at least one first kind of binding domain is a naturally occurring binding domain that binds to an organic receptor, and at least one second kind of binding domain that is not naturally present in the adhesin which is capable of binding to a compound to which the naturally occurring adhesin protein substantially does not bind, wherein the second kind of binding domain is provided by inserting into the gene coding for said adhesin a DNA sequence coding for a metal binding peptide sequence, selected from the group consisting of a Cr, Pb, Mn, Ni, Co, Zn, Hg and a precious metal compound.

However, Sousa et al. teaches the use of "A number of systems that employ outer membrane proteins, lipoproteins, and flagellar proteins of Gram-negative bacteria as anchor sites for peptides have become available over the last few years" (p. 1017, 1st column, 1st paragraph), and further exemplifies the engineering of recombinant bacterial cells to have increased metal binding affinity by inserting one or two hexa-histidine clusters in a protein of the outer membrane, to provide the ability to act as a metalloaffinity adsorbent by binding to Ni containing compounds (see abstract, p. 1017-1019).

It would have been obvious to one of ordinary skill in the art to have modified the adhesin protein disclosed by Pallesen by inserting a hexa-histidine cluster, as disclosed by Sousa et al., to form a second binding region which increased metal affinity, since both Pallesen et al. and Sousa et al. disclose the modification of binding proteins on the outer surface of a cell, in order to alter its binding properties to recognize a compound of interest. One would have been motivated to do so by the teaching of Sousa et al. regarding the usefulness and desirability of such a protein having metal binding properties for such uses as biosorption of heavy ions using engineered microorganisms. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-4, 6-10, 12-15, and 18-22, 24, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pallesen et al. (Microbiol., 141: 2839-2848, 1995) as applied to claims 1-4, 6, 8, 9, 12-15 and 18 above, in view of Georgiou et al. (Nature Biotechnol., 15: 29-34, 1997) (both cited by applicants).

Pallesen et al. is cited for the reasons set forth above.

Pallesen et al. does not disclose a population of recombinant cells expressing on their surface a multifunctional adhesin protein containing at least one first kind of binding domain is a naturally occurring binding domain that binds to an organic receptor, and at least one second kind of binding domain that is not naturally present in the adhesin which is capable of binding to a compound to which the naturally occurring adhesin protein substantially does not bind, comprising a multiplicity of clones of said cells that comprises at least 10^6 different clones, and methods of constructing said population as recited in claims 20-25. It is noted that Pallesen et al. suggests the possibility of making such a population for the display of randomly created peptide libraries (p. 2847, last paragraph).

However, Georgiou et al. teaches populations of recombinant cells comprising a multiplicity of clones of a cell expressing on their surface peptides inserted into a surface protein such as a flagellum, and methods of constructing said populations comprising the steps of constructing a random library of DNA sequences coding for peptides, inserting the library into a gene coding for a surface protein, and transforming a host cell population with the library (see pages 30–31). The reference discloses enriching the cell population for cells specifically binding to a particular compound to which the surface protein without modification substantially does not bind comprising contacting the cell population with said compound whereby cells expressing a second kind of binding domain that is capably of binding to the compound aggregates with said compound, separating the cell-compound aggregates and isolating cells capable of binding to the compound (see page 30-31). The reference discloses said method using iterative or recursive screening techniques (page 31).

It would have been obvious to one of ordinary skill in the art to have modified the cell production method of Pallesen et al., to include a larger population of the generated recombinant cells as a library as disclosed by Georgiou et al., since both Pallesen et al. and Georgiou et al. disclose methods of constructing recombinant cells that display peptides of interest in such surface structures as pilli and flagella, said peptides having binding abilities, for the purpose of binding to a compound of interest. One would have been motivated to do so by the desire to display a library of random peptides on the surface of a cell, for a purpose such as screening for peptides with specific binding properties, as disclosed by Georgiou et al. and suggested by Pallesen et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-4, 6-10, 12-15, and 18-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pallesen et al. (Microbiol., 141: 2839-2848, 1995) as applied to claims 1-4, 6, 8, 9, 12-15 and 18 above, in view of Georgiou et al. (Nature Biotechnol., 15: 29-34, 1997) (both cited by applicants) and further in view of Sousa et al. Sousa et al. (Nature Biotechnol., 14: 1017-1020, 1996).

Pallesen et al. and Georgiou et al. are cited for the reasons set forth above.

The difference between the references and the instant claim is that the cells are enriched for binding to a metal compound.

However, Sousa et al. discloses "outer membrane proteins, lipoproteins, and flagellar proteins of Gram-negative bacteria as anchor sites for peptides have become available over the last few years" (p. 1017, 1st column, 1st paragraph), and further exemplifies the engineering of recombinant bacterial cells to have increased metal binding affinity by inserting one or two hexa-histidine clusters in a protein of the outer membrane, to provide the ability to act as a metalloaffinity adsorbent by binding to Ni containing compounds (see abstract, p. 1017-1019).

It would have been obvious to one of ordinary skill in the art to have utilized the method disclosed by Pallesen et al. in view of Georgiou et al., to enrich for cells that specifically bind to a compound such as a metal compound, such as the cells disclosed by Sousa et al. since Pallesen et al., Georgiou et al. and Sousa et al., all disclose methods of inserting peptides into surface display molecules in cells, and using said cells for the specific binding to compounds of interest. One would have been motivated to do so by disclosure of Sousa et al. that such cells are useful for disclose the modification of binding proteins on the outer surface of a cell, in order to alter its binding properties to recognize a compound of interest. One would have been motivated to do so by the teaching of Sousa et al. regarding the usefulness and desirability of such a protein having metal binding properties for such uses as biosorption of heavy ions using engineered microorganisms. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Sokurendo et al. (J. Bacteriol., 177(13), p. 3680-3686, 1995) in view of Pallesen et al. (Microbiol., 141: 2839-2848, 1995) (cited by applicants).

Sokurendo et al. disclose cells comprising the fimbriae comprising the FimH adhesin, which differs from the PC31 FimH adhesin by at least one amino acid whereby its saccharide binding characteristics is changed relative to those of the E. coli PC31 FimH adhesin (see Figs. 1, 4, see Table 1). The reference discloses that these cells are isolated from different host niches.

The difference between the reference and the instant claim is that the FimH adhesin is modified by the inclusion of a second kind of binding domain that is not naturally present in the adhesin protein.

However, Pallesen et al. disclose Pallesen et al. describes recombinant cells expressing on its surface a multifunctional adhesin protein (FimH adhesin), containing at least one first kind of binding domain is a naturally occurring binding domain that binds to an organic receptor, and at least one second kind of binding domain that is not naturally present in the adhesin , which is capable of binding to a compound to which the naturally occurring adhesin protein substantially does not bind. The reference discloses peptide insertion into the extracellular domain to create new binding domains "without affecting compatibility with the ... adhesive ability" (p. 2840, 2nd column, 2nd paragraph) as recited by claims 1-4 and 12-14. The reference discloses the non-naturally occurring binding region is that of preS2 sector of the hepatitis B surface antigen or the epitope from cholera toxin (p. 2840, 2nd column, 2nd paragraph.

It would have been obvious to one of ordinary skill in the art to have modified any of the variant strains of E. coli disclosed by Sokurenko et al., to include in the FimH adhesin, a second binding domain, apart from the first binding domain, in order to obtain a multifunctional adhesin protein, since both Sokurendo et al. and Pallesen et al. disclose that the E. coli cells therein comprise a fimbriae comprising the protein FimH, which is responsible for adhesion specificity. One would have been motivated to do so by the desire to obtain recombinant cells comprising multifunctional adhesin proteins having various useful binding properties, since Pallesen disclose the usefulness of such strains in such methods as general display systems and the presentati9on of relevant epitopes for vaccine purposes. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 12-15, 18-20, and 22-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection is based on the Guidelines for the Examination of Patent Applications under the 35 U.S.C. 112, first paragraph "Written Description published in the Federal Register (Volume 66, Number 4, Pages 1099-1111). The claims are drawn to recombinant cells expressing on the surface a multifunctional adhesin protein, which may be any naturally occurring adhesin protein containing a first kind of binding domain capable of binding to an organic receptor and a second kind of binding domain which is not naturally present in the adhesin protein from which the multifunctional adhesin protein is derived, and is capable of binding to a compound to which the naturally occurring adhesin protein substantially does not bind. The specification has not defined what is intended by the term "derived from", however, the specification discloses that any modification of the naturally occurring binding site, in addition to the insertion of any second, non-naturally occurring binding site, at any region of the adhesin protein, resulting in two binding sites, are encompassed. Claims 1, 2, 12-15, 18-20, and 22-25 are genus claims in terms of recombinant cells comprising any adhesin protein, including fimbriae or pilli, which comprising two kinds of binding domains, one of which is not naturally present in the adhesin protein, and one which may be the naturally occurring binding domain or a modification thereof. The claims encompass a broad class of recombinant cells comprising modified, multifunctional adhesin proteins. The disclosure is not deemed to be descriptive of the complete structure of a representative number of species encompassed by the claims as one of skill in the art cannot envision all the recombinant cells comprising multifunctional adhesin proteins based on the teachings of the specification. While the specification provides general information on regions of the FimH proteins into which a binding domain may be inserted with retention of function of both the newly inserted domain and the first, naturally occurring domain, there is no similar analysis of other proteins. Therefore, the specification does not describe the claimed recombinant cells expressing a any multifunctional adhesin protein, containing at least two kinds of binding domain, including the second kind that is not naturally present in the adhesin protein from which the multifunctional adhesin protein is derived and is capable of binding to a compound to which the naturally occurring adhesin protein substantially does not bind in such full, clear, concise and exact terms so as to indicate that Applicant has possession of the recombinant cells at the time of filing the present application. Thus, the written description requirement has not been satisfied.

Vas-Cath V. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is now claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of recombinant cells comprising multifunctional adhesin protein made from any naturally occurring adhesin protein, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation or identification. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Col. Ltd.*, 18USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only recombinant cells comprising a multifunctional adhesin protein which is the FimH protein, modified by the addition of a second kind of binding domain that is not naturally present in the FimH protein, and having a first kind of binding domain which may or may not be the naturally occurring binding domain, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

Claim 1,3, 22 and by dependence claims 2, 4-15, 18-21, 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, and 22 and by dependence claims 2, 4-15, 18-21 and 23-25 are vague and indefinite in the recitation of "derived from", since it is not known what the number and types of steps involved in the "deriving" are.

Claim 2 is vague and indefinite in the dependence on "claim 2". Presumably, it is meant to depend from claim 1. The claim has been examined as if this were recited.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NANCY VOGEL, PH.D.
PATENT EXAMINER